959-49 Are ACTs Helpful in the Management of Anticoagulation With Low Molecular Weight Heparin?

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Enoxaparin (Enox) has been approved for prophylaxis for venous thromboembolism and has shown promise in unstable angina and post coronary stent placement. The ratio of anti-Xa:anti-IIa activity for Enox (3:1) is higher than with heparin (1:1). Both aPTT and activated clotting time (ACT) are used to monitor anticoagulation with heparin. ACTs are now standard for monitoring anticoagulation during acute coronary intervention. At doses up to 90 mg, SQ Enox does not prolong the aPTT but the effect on ACT is unknown. TIMI 11a was a multicenter dose-ranging trial (1.0–1.25 mg/kg SQ q12 hrs) to evaluate the safety and tolerability of Enox in patients with unstable angina/non-Q wave MI. We obtained peak (mean 4.3 hrs post-Enox) and trough (mean 11.5 hrs post-Enox) anti-Xa levels and ACTs for 26 patients in the TIMI 11 a trial as shown below. Despite large doses of Enox (89 ± 19 mg q12 hrs) and significant increases in anti-Xa levels even at the trough, there was no change in ACT measured by Hemotec and only a small increase with Hemachron. In addition, the correlation of peak Hemachron ACT with peak anti-Xa levels was poor (R = 0.5, P = 0.08). *Conclusion:* In contrast to heparin, ACTs are not adequate for assessment of anticoagulation with Enox. Therefore, ACTs should not be relied upon in patients on Enox who require acute coronary intervention or additional anticoagulation with heparin.

	n	Trough	Peak	Normals (No Anticoagulation)
	n			
Hemotec ACT	15	127 ± 21	127 ± 9	127 ± 16
Hemachron ACT	11	135 ± 19	152 ± 28*	126 ± 25
Total ACT	26	131 ± 20	138 ± 23	
Anti-Xa	26	0.51 ± 0.28	1.3 ± 0.40**	0.0

A" data: mean ± SD. *p < 0.05 vs. normal, ** p < 0.0001 vs. trough

959-50 Dofetilide Decreases Defibrillation Threshold, But not in Proportion to its Prolongation of Refractoriness and QT Intervals

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We tested the hypothesis that dofetilide causes a reduction in defibrillation threshold (DFT) that is inversely proportional to the changes it causes in the effective refractory period (ERP) and QT intervals. In 12 pigs, two platinum spring electrodes were placed in the RV apex and the RV-SVC junction. Six pigs were studied using three cumulative doses of dofetilide (2.5, 7.5 and 15 μg/kg bolus +0.9, 3.6 and 9 μg/kg/hr maintenance, respectively). Six control pigs were given saline. DFTs were determined using an up/down protocol by giving fixed-duration (10 ms), single capacitor (150 μF) biphasic shocks (6 ms phase 1). LV-ERP measurements were made with endocardial stimuli and QT intervals were obtained from surface ECG lead II. Ventricular fibrillation cycle lengths (VF cl) were measured from LV endocardial electrograms. *p < 0.05 vs Baseline.

Dofetilide	Dose (μg/kg)	DFT (V)	ERP (ms)	QTc (ms)	VF cl (ms)
Baseline	0	373 ± 81	185 ± 16	430 ± 21	88 ± 7
Low	2.5	337 ± 80*	210 ± 14	450 ± 21	99 ± 11*
Mid	7.5	349 ± 54	218 ± 14*	459 ± 12*	107 ± 13*
High	15	368 ± 87	242 ± 39*	465 ± 30	110 ± 18*

There was no significantly difference for the above parameters in the control group.

Conclusion: Dofetilide significantly reduces DFT only in its low dose in pigs and the effect on DFT is not monotonically related to its effect of prolongation of ERP and QT intervals. Thus: (1) only a small DFT effect of dofetilide occurs in pigs, which differs from dogs studied by others and (2) the decrease in DFT is not related in a 1:1 manner with increase in ERP.

960 Adhesion Molecules

Monday, March 17, 1997, 3:00 p.m.–5:00 p.m.
Anaheim Convention Center, Hall E
Presentation Hour: 4:00 p.m.–5:00 p.m.

960-109 Deficiency of Cell Adhesion Molecules Protects Against Atherosclerosis in Mice

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Leukocyte and endothelial cell adhesion molecules (CAM) are essential for emigration of leukocytes. Based on the evidence for an increased expression of CAM in atherosclerotic lesions, we tested the hypothesis that reduced expression of CAM might be protective against the disease. Using C57BL/6 female mice which develop atherosclerotic fatty streaks on high fat diet, animals which were homozygous or wild type for the CAM mutation were started on high fat diet at the age of 12 weeks, and after 20 weeks on diet, they were sacrificed. Hearts were removed and fixed, and atherosclerotic lesions quantified using standard methods. Compared to wild type, the reduction in the lesions was as follows: 47% for the CD18 deficient mice, (P < 0.03), 63% reduction for the ICAM-1 deficient mice (P < 0.0003), 63% for the P-selectin deficient mice (P < 0.0001), 76% for the combined CD18/ICAM-1 deficient mice (P < 0.0001), and 71% for the combined ICAM-1/P-selectin group (P < 0.0002). Lipid analysis revealed significant differences only in the P-selectin groups, which had higher HDL levels than the control group. The above data provide the strongest evidence to date for a direct cause and effect role for CAM in the development of atherosclerosis, and suggests that genetic variation in CAM could affect susceptibility to the disease, and that pharmacologic reduction in the expression or function of CAM might be protective against atherosclerosis.

960-108 Expression of Adhesion Molecules on Microvessels in Advanced Human Atherosclerotic Plaques: Alternative Pathways for Leukocyte Recruitment

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The presence of activated macrophages and lymphocytes is a characteristic feature of atherosclerotic (AS) plaques. T cells migrate into the lesions after specific interactions with adhesion molecules expressed by endothelial cells (EC) and leukocytes. Up till now, most studies on the expression of adhesion molecules focused on arterial EC, but advanced AS lesions have regions with neovascularised areas (microvessels), and in these areas often large infiltrates with immunocompetent cells can be found. Recently, a novel endothelial activation marker was described: CD40, member of the tumor necrosis factor receptor family of adhesion receptors. Cytokines are capable to upregulate CD40 on EC. After ligation with its ligand, CD40 increases the expression of other adhesion molecules such as VCAM-1 and E-selectin, and, therefore, may play a regulatory role in the recruitment of immunocompetent cells in AS lesions. In this study, we examined the expression of CD40, VCAM-1, E-selectin and ICAM-1 on microvascular EC in human carotid endarterectomy specimens (n = 8) using immunohistochemical single and double staining techniques. We found that all microvessels in human AS plaques are ICAM-1 positive, and focally EC also express VCAM-1 and E-selectin. Focal expression of CD40 was observed on subpopulations of microvascular EC. Not all activated vessels (VCAM-1$^+$, E-selectin$^+$) were CD40 positive, as demonstrated with immunohistochemical double staining techniques. This study shows that microvascular EC are likely to be involved in the recruitment of immunocompetent cells in AS lesions.

960-110 Temporal and Spatial Variation in Alpha v Beta 3 Integrin Expression Following Deep Arterial Injury in the Porcine Coronary Restenosis Model

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Background: Cell-matrix interaction via integrin $\alpha_v\beta_3$-ligand (osteopontin, vitronectin) interaction has been shown to mediate the adhesion and migration of smooth muscle cells (*SMC*) and endothelial (*EC*) cells in vitro. Less is known about the in-vivo expression of $\alpha_v\beta_3$ in vascular restenosis. *Methods:* Using a mouse monoclonal antibody to $\alpha_v\beta_3$ (*LM609*) we studied its expression at serial time points following oversized coronary arterial stent

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